REMARKS

Claims 1, 7, 12, 13, 16, 27, 28, 33, and 35-36 are amended herein. Claims 9-11, 15, and 23-26 are canceled herein. Claims 17, 20-22 and 32 were previously canceled. Claims 18, 19 and 29-31 are withdrawn from consideration.

No new matter is presented.

Upon entry of the Amendment, claims 1, 7-8, 12-14, 16, 27-28 and 33-36 will be all of the claims pending in the application for examination.

I. Response to Claim Rejections - 35 U.S.C. § 103

A. Hasegawa et al or JP 8291106 in view of Ohuchida et al, Black, Toda et al and Takada et al

Claims 1, 7-16, 23-28, and 33-36 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Hasegawa et al (Bull. Chem. Soc. Jpn. 2000, 73, 423-428) or JP 8291106 in view of Ohuchida et al (US 6,201,021), Black (US 6,043,223), Toda et al (US 6,608,221) and Takada et al (US 2002/0022738 Al).

Applicants respectfully traverse the rejection for the reasons of record, which are incorporated herein by reference and in view of the following.

The Examiner essentially maintains his previous position and addresses Applicants' claim amendment to recite that the liquid medicament is a micelle water dispersion by merely allegedly that the composition of the prior art and their conditions are similar to Applicants' composition and, therefore, it is expected to have micelle water dispersion of liquid.

Applicants maintain that the Examiner's position is not reasonable regarding the combination of references and the reasons therefore.

The Examiner' position with respect to the amended claims is even more unreasonable since the Examiner's position is based on inherency and the Examiner can not point to a single composition disclosed by any of the references which is similar to that of the present invention. First, one of ordinary skill would not combine or modify the references as suggested by the Examiner for the reasons already presented. Further, assuming *arguendo* that the cited references could be combined as suggested, by the Examiner, the claimed invention would not have been achieved. The Examiner's position is based primarily on improper hindsight reconstruction and the Examiner has not provided a reasonable technical basis for asserting that, even if the references could be combined, a micelle water dispersion liquid would be obtained.

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " MPEP § 2112(IV).

In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. In this case, the Examiner has not met this burden.

The Examiner relies on 6 different references, none of which teach the combination of the claimed (2R)-2-propyloctanoic acid or salt thereof and a basic metal ion supplied by at least one selected from a metal salt of phosphoric acid, a metal salt of carbonic acid and a metal salt of sulfuronic acid, much less having about 1 to 5 equivalents of a basic metal ion based on 1 equivalent of (2R)-2-propyloctanoic acid or salt thereof.

Further, the Examiner admits that Black teaches the use of sodium hydroxide to dissolve zaprinast and there is no teaching or suggestion of mixing (2R)-2-propyloctanoic acid with sodium phosphate. The Examiner also admits that Takada et al does not teach any similarity between its drug compound and (2R)-2-propyloctanoic acid or salt thereof. Additionally, Applicants have pointed out that more than 12,0000 times of the basic metal ion based on 1 equivalent of the active ingredient are included in the preparation of Black, whereas Applicants' claim a very narrow range of about 1 to about 5 equivalents of the basic metal ion based on 1 equivalent of (2R)-2-propyloctanoic acid or salt thereof. Neither of Hasegawa et al nor Hisao et al teaches or suggests a medicament comprising (2R)-2-propyloctanoic acid and a basic metal ion and Toda et al does not relates to a process which is not related to the claimed invention.

The cited references are completely silent as to the feature of a micelle water dispersion liquid of components (a) and (b). Yet, despite the facts that (1) there is no teaching, suggestion or mention of a micelle water dispersion liquid in any one of the six references; (2) there are

several acknowledged differences between the claimed invention and the cited art; and (3) there is not one embodiment of a similar composition to that of the claimed invention in the cited references, the Examiner asserts that the "composition of the cited prior art" is expected to have micelle water dispersion of liquid of the compound.

The Examiner refers to Applicants' specification in support of his position in stating that the specification discloses that micelles, i.e., aggregates formed by (2R)-2-propyloctanoic acid or aggregates formed from the interaction of (2R)-2-propyloctanoic acid with a basic metal ion, are homogeneously dispersed in the medium and its properties are not significantly different from those of conventional aqueous solutions.

However, the specification refers to the property of "fluidity or the like" of the micelle water dispersion liquid. See page 23, lines 1-5. This disclosure in the specification means that although the micelle water dispersion liquid contains aggregates, it maintains fluidity properties similar to those of conventional aqueous solutions and, therefore, is still useful as a liquid medicament for preparing injections as claimed. It would not be desirable to have a micelle water liquid dispersion for preparing an injection solution, which has fluidity properties that significantly different from those of conventional aqueous solutions. Thus, the feature of a micelle liquid dispersion of components (a) and (b) indicates a distinct physical property of the claimed invention which is not taught or suggested by the prior art. Nor does the prior art recognize the advantages of such a feature, which allows for high concentrations of (2R)-2-propyloctanoic acid while maintaining operability equal to that of aqueous solutions. See page 23 of the specification, lines 6-11. For at least this reason, the present invention is not rendered obvious by the cited references, whether taken alone or in combination.

Moreover, the present invention provides unexpectedly superior results over the prior art. As shown by the attached Declaration, the present invention has the following remarkable effects that: (1) (2R)-2-propyloctanoic acid, which is insoluble in water, can be dissolved in water in high concentrations in the medicament of the present invention; (2) the medicament of the present invention has resistance to pH fluctuations using solution and/or dilution liquid before use; and (3) it is possible to prepare an infusion which has a pH that can be administered to patients without clouding. Such remarkable effects could not have been expected based on the cited references. For this additional reason, the present invention is patentable over the cited references.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Honjo et al in view of Nakaoka et al and Takada et al

Claims 1, 7-16, 23-28, and 33-36 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Honjo et al (EP 1 415 668 A1) in view of Nakaoka et al (JP 07285911 A) and Takada et al (US 2002/0022738 A1).

Applicants respectfully traverse the rejection.

First, with regard to the newly cited reference Nakaoka et al, the invention of Nakoaka et al relates to "aliphatic monocarboxylic acid composition comprising one or more kinds of aliphatic monocarboxylic acids of formula R-COOH in combination with one or more kinds of inorganic salts selected from metal phosphates, metal phosphinates and metal sulfites". Namely, the invention of Nakaoka et al relates to a composition which is superior in heat-resistance (metallic soap). In paragraph [0017] of the publication, there is description that "Although

mixing amount of inorganic metal salt is not limited as long as a predetermined effect is acquired, it is usually 5-10,000 ppm to aliphatic monocarboxylic acid. It is hard to obtain a remarkable heat-resistance improvement effect in less than 5 ppm while in case of exceeding 10,000 ppm, the effect does not increase and is uneconomical, and moreover inorganic metal salt may not dissolve thoroughly. Neither of the cases are preferable."

In this connection, the unit of "ppm" means millionth. Additionally, it is clear from the description in Example 1 that "200 g of stearic acid was prepared and dissolved at temperature at 70 °C, followed by addition of 0.02g of disodium hydrogenphosphate (100 ppm per stearic acid)", it can be known that "ppm" in the present specification is millionth based on weight.

On the other hand, in the present application, inorganic metal salts (1 to 5 equivalent(s)) which are added to 1 mol (=186.29 g) of (2R)-2-propyloctanoic acid is at least about 50 g and about 600 g at most as described at page 18, lines 20-24. In this connection, since molecular weight of (2R)-2-propyloctanoic acid is 186.29, the amount of the inorganic metal salts can be calculated to be about 270,000 ppm to about 3,220,000 ppm in case where the amount is expressed by ppm.

As it can be known by the magnitude of the amount, a far greater amount of inorganic metal salts is added in the present application in comparison with Nakaoka et al. Additionally, contrary to Nakaoka et al, the phenomenon described that "inorganic metal salt is not completely dissolved" is not observed in the present invention.

In Takeda et al, a method for adding a pH adjuster selected from tri-sodium phosphate, a hydrate thereof, sodium hydroxide or potassium hydroxide to solution in order to improve solubility of drug is disclosed.

Additionally, in Honjo et al, a pharmaceutical composition of the compound of formula (I) for the treatment of brain ischemic diseases is disclosed. The formula (I) includes (2R)-2-propyloctanoic acid. Furthermore, a method for producing salts of the compound of formula (I) is disclosed and alkali metal salts and alkaline earth metal salts are described as preferable salts.

However, the equivalent number of basic metal ion, which is an essential feature of claims in the present application, is not disclosed in either of Takeda et al or Honjo et al. Additionally, in Nakaoka et al, wherein the mixing ratio of aliphatic monocarboxylic acids and inorganic metal salts is disclosed, a far less equivalent number is described in comparison to the present invention. In the cited references, the problems of (2R)-2-propyloctanoic acid which should be solved (clouding in dilution and stability during storage) are not disclosed at all. Even if these problems were known, one of ordinary skill in the art would not have considered adding metal salts in an amount which far exceeds the concentrations disclosed in Nakaoka et al in order to solve the problems.

Even further, the cited references fail to teach or suggest "a micelle water dispersion liquid" as claimed.

With respect to the Examiner's assertion that Honjo teaches a composition similar to that of Applicants' claimed invention, Honjo generally teaches a composition comprising an astrocyte-function improving agent, preferably (2R)-2-propyloctanoic acid, and an antithrombolytic). The only description of a specific embodiment of the composition of Honjo et al is in Example 1 of t-PA (i.e., an antithrombolytic) and (R)-2-propyloctanoic acid (i.e., astrocyte function improving agent).

However, Honjo does not disclose a basic metal ion as part of the composition, much less the amount of basic metal ion. Further, Honjo is silent as to the feature of a micelle water dispersion liquid and it can not be said that this feature is inherent in the composition of Honjo. There is no teaching or suggestion of this feature and the compositions do not contain the same components in the same amount as claimed. Thus, the Examiner has not met his burden of establishing that the composition of Honjo *necessarily* meets the element of a micelle water dispersion liquid.

Neither of Nakaoka nor Takada remedy this deficiency since these references also fail to disclose, teach or suggest a similar composition having the same components and same amount or the feature of a micelle water liquid dispersion. Additionally, one of ordinary skill in the art would not have been motivated to combine the references as suggested by the Examiner, Nakaoka is directed to compositions having improved heat-resistance and useful as a raw material for metallic soap and for various esters. One of ordinary skill in the art would not have been motivated to therefore combine Honjo directed to a pharmaceutical composition for the treatment of cerebral ischemic diseases and Nakaoka which is directed to forming a raw material for metallic soap and various esters with a reasonable expectation of success in achieving the claimed invention. Further, Takada do not teach or suggest any similarity between the drug compound of Takada et al and (2R)-2- propyloctanoic acid or salt thereof. Thus, one of ordinary skill in the art would not have been motivated to combine the references as suggested by the Examiner. Even if the references were combined the claimed invention would not have been achieved.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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Date: November 29, 2010